Anionic Ring-Enlarging Reaction of a Hemiaminal System: Stereoselective Approach to Disubstituted Tetrahydroisoquinolone

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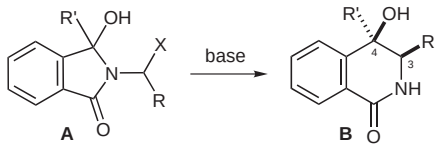
Abstract: Treatment of N-substituted phthalimide-derived hemiaminal with alkyllithium led to tetrahydroisoquinolones with high diastereoselectivity. Mechanistic studies furnish persuasive evidence that the present ring-enlarging reaction proceeds via tautomerization of the hemiketal moiety and the resulting ketone undergoes an intramolecular nucleophilic addition reaction.

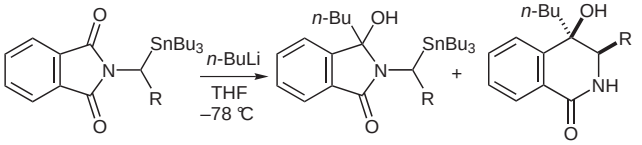
Key words: hemiaminal, α-aminocarbanion, stereoselective synthesis, tetrahydroisoquinolone, axial chirality

Substituted tetrahydroisoquinolones are valuable compounds as synthetic precursors for a large and diverse family of biologically important alkaloids.[1] Although several methods for the stereoselective synthesis of substituted tetrahydroisoquinolones have been reported, a more efficient approach needs to be developed.[2] Herein, we wish to report a stereoselective approach to *syn*-3,4-disubstituted tetrahydroisoquinolones **B** by an anionic ring-enlarging reaction of phthalimide-derived hemiaminal **A** (Scheme 1). We found this simple and efficient approach while studying α-amino alkylstannanes.[3]



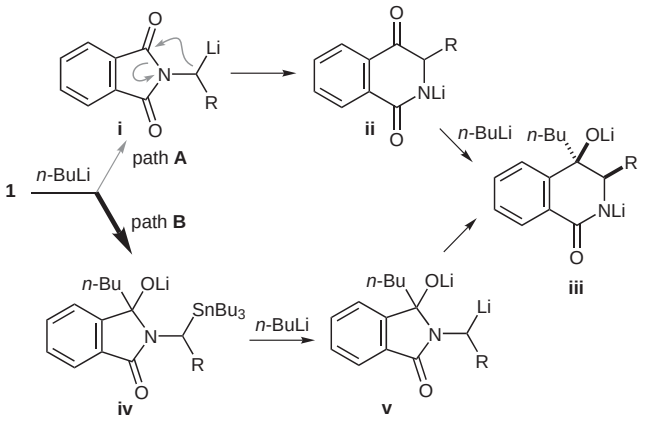
Scheme 1

Recently, we synthesized a phthalimide-derived α-amino alkylstannane **1** to study the aza-Wittig rearrangement.[3a] To further explore the synthetic utility of this class of compounds, we planned ring-enlarging acyl migration of alkyllithium **i** prepared from **1** via Sn→Li transmetallation (vide infra: path **A** in Scheme 3).[4] However, the reaction of stannane **1** with an equimolar of *n*-BuLi in THF at –78 °C gave hemiaminal **2** exclusively (88%), instead of the expected ring-enlarged product.[5] Nevertheless, a similar reaction using two equivalents of *n*-BuLi gave tetrahydroisoquinolone *syn*-**3** in 46% yield as a single diastereomer,[6] along with hemiaminal **2** (18%; Scheme 2). These results clearly indicated that nucleophilic addition of *n*-BuLi to the imido-carbonyl is much faster than Sn→Li transmetallation and that the ring-enlarging reaction proceeds via dilithiated hemiaminal **v** as shown in path **B** (Scheme 3).



1	*n*-BuLi	2	*syn*-**3**
R = PhC_2H_4	1.0 equiv	88%	n.d.
	2.0 equiv	18%	46% (dr = >99:<1)

Scheme 2



Scheme 3

Based on this observation, we envisaged that the non-stannylated phthalimides, bearing an acidic α-amino proton, can also provide tetrahydroisoquinolones via **v** by the action of an excess amount of organolithium as a base. As expected, the reaction of *N*-benzyl-phthalimide (**4**) with five equivalents of *n*-BuLi in THF gave tetrahydroisoquinolone **5a**, although the chemical yield was moderate (Scheme 4). Significantly enough, a similar reaction using MeLi provides the corresponding ring-enlarging product **5b** in excellent yield with a high level of *syn*-selectivity (98% yield, dr = 95:5).[7] This result reveals that MeLi is a superior base for the present ring-enlarging reaction.[8]

In order to access a wider variety of tetrahydroisoquinolones, next we performed a ring-enlarging reaction of hemiaminal **6** containing various R′ groups.

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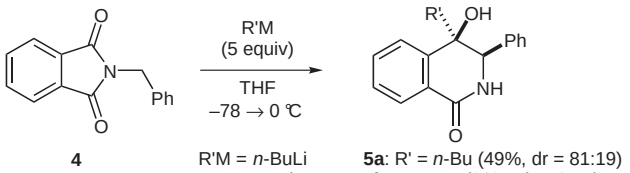
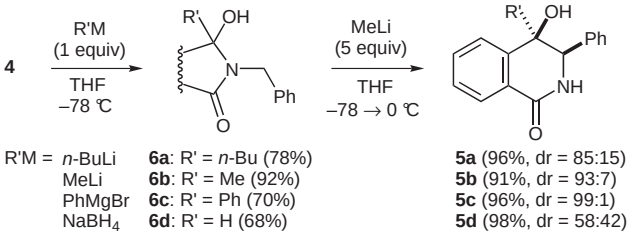


Scheme 4



Scheme 5

Hemiaminals **6a**–**d** were easily prepared from **4** with the corresponding R′M reagents, and they provide tetrahydroisoquinolones **5a**–**d** upon treatment with MeLi in excellent chemical yields as shown in Scheme 5.[9,10]

The present ring-enlarging reaction most probably proceeds via tautomerization of the hemiketal moiety and the resulting ketone undergoes an intramolecular nucleophilic addition reaction (path **A** in Scheme 6).

An equally likely aza-[1,2]-Wittig rearrangement pathway (path **B** in Scheme 6)[11] was ruled out by the result of a comparable experiment with **6b**-derived methyl aminal **7** and deoxygenated-derivative **8** (Figure 1). They are reasonable substrates for aza-Wittig rearrangement; however, they gave no ring-enlarging product under similar conditions.[12] It clearly shows the hemiketal moiety is essential in the present ring-enlarging reaction.

It is interesting to note that the hemiaminal alkoxide acts as a masked ketone, and reacts only with an intramolecular nucleophile (benzylic carbanion) but does not react with the excess alkyllithium.

To validate the proposed mechanism and to gain an insight into the high *syn*-selectivity, we performed a computational study of simplified model compound **9** using density functional theory (DFT) calculations (Figure 2).[13]

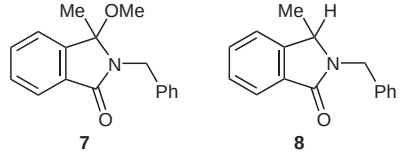
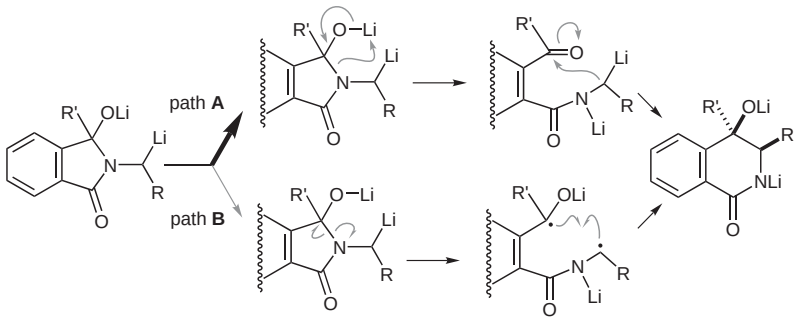


Figure 1

First, the expected transition states TS1 (6.0 kcal mol^{-1}) for isomerization of dilithiated hemiaminal **9** and TS3 (14.2 kcal mol^{-1}) for intramolecular nucleophilic addition leading to **10** (–16.0 kcal mol^{-1}) were optimized from the predicted geometries near the saddle points. Second, intrinsic reaction coordinate (IRC) analyses of the thus-obtained TS1 and TS3 were performed to demonstrate the adequacy of their structures, as well as to find the structure of the intermediates. Interestingly enough, IRC calculation of TS1 gave **9** and IM1 (–9.9 kcal mol^{-1}) as the two stable conformations; in the meantime, TS3 gave **10** and IM2 (–5.7 kcal mol^{-1}). These results indicate that the present ring-enlarging reaction proceeds via at least three steps. Finally, the transition state TS2 (17.4 kcal mol^{-1}) for the transformation of IM1 to IM2 was found to have the highest energy barrier in this reaction pathway.

The reaction profile shows that this reaction is constructed from the three steps, and the intermediate IM1 is transformed into IM2 so the reaction points are in close proximity (C^1 and $C^{1'}$) along with Li^1 and Li^2 which change their counter anion from N to $C^{1'}$ and $C^{1'}$ to N, respectively. Next, the transition states of $C^{1'}$-methyl-substituted model compound **11** were calculated, in a similar manner, to clarify the origin of the *syn*-selectivity in this reaction (Scheme 7).

As a result, the *anti*-selective transition state at the third step (*anti*-TS3) shows a significantly higher energy barrier (16.7 kcal mol^{-1}) than that of the *syn*-selective transition state (*syn*-TS3, 8.0 kcal mol^{-1}). The steric repulsion of substituents on C^1 and $C^{1'}$ carbons increases the activation energy of the transition state *anti*-TS3 so that the *syn*-product is predicted to be formed as the major diastereomer through the transition state *syn*-TS3. Encouraged by the establishment of a highly *syn*-selective ring-enlarging reaction, we next performed a similar reaction using enantio-enriched stannane **1**. To our surprise, the optical purity of *syn*-**3** obtained from (*R*)-**1** (>95% ee) was only 33% ee,



Scheme 6

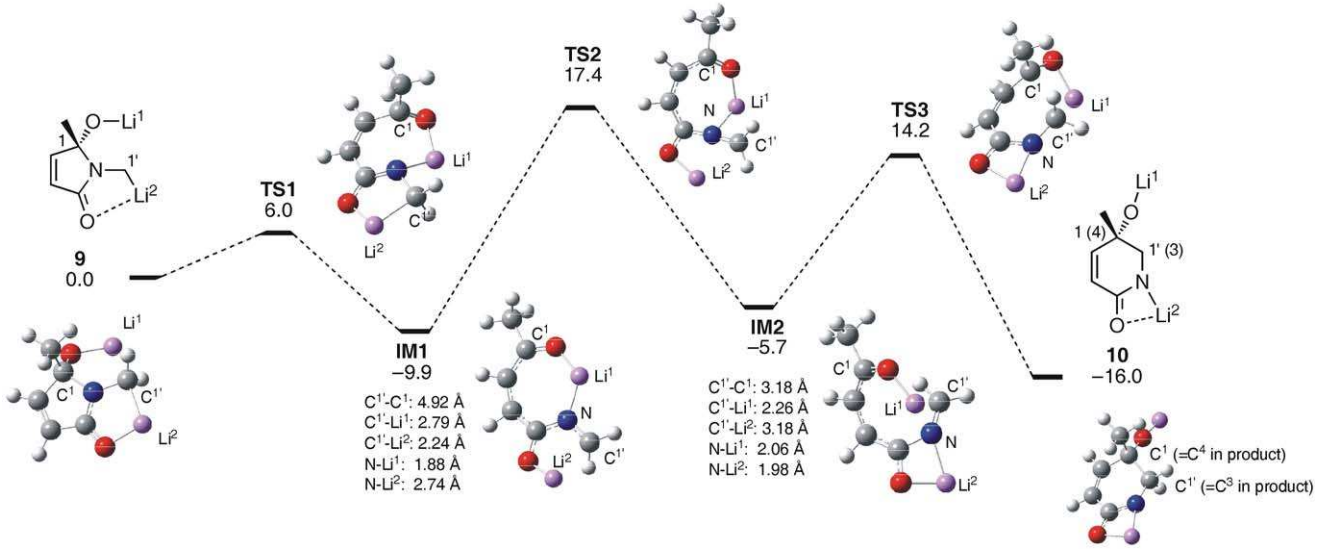
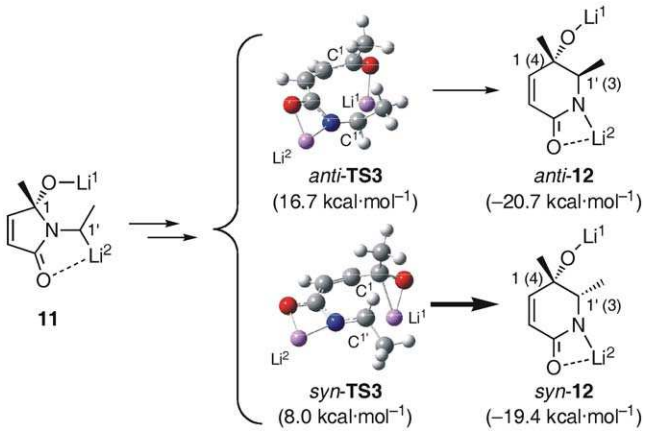
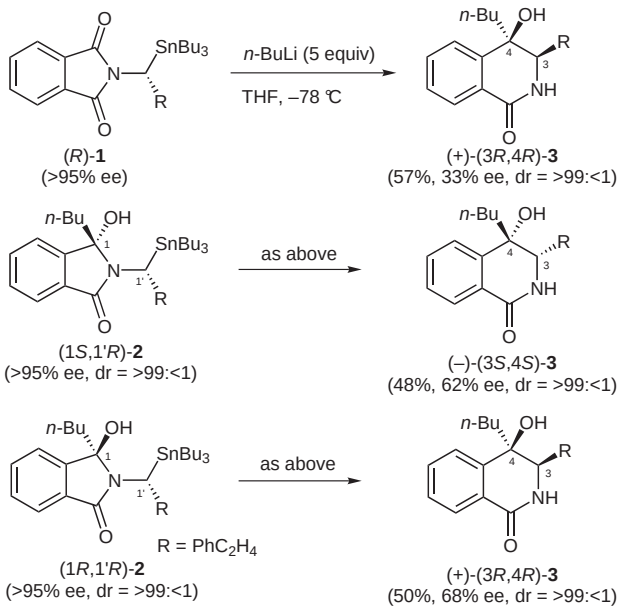


Figure 2 B3LYP/6-31+G(d) potential energy surface of the ring-enlarging reaction of dilithiated hemiaminal **9** (energies in kcal mol^{-1}).



Scheme 7 Transition states of intramolecular addition reaction (TS3) for dilithiated hemiaminal **11** [B3LYP/6-31+G(d)].



Scheme 8

which means that the reaction proceeds in a non-stereospecific manner in terms of α-amino carbanion chirality.[14,15] On the contrary, the reaction of both diastereomers of hemiaminal **2**, namely (1*S*,1′*R*)-**2** and (1*R*,1′*R*)-**2**, provides *syn*-**3** maintaining surprisingly high optical purity (62–68% ee). Of particular note, is that their major enantiomer has the opposite sign of rotation (Scheme 8).[16] The above-mentioned stereochemical outcome is attributable to the axial chirality on the carbonyl moiety in **vi** or *ent*-**vi** derived from the central chirality of C^1 and it exerts a stronger influence than that of the α-amino carbanion chiral center (C$^{1'}$) on the steric course of the reaction. Then the reaction of (1*S*,1′*R*)-**2** preferentially proceeds via **vi** to provide (3*S*,4*S*)-**3**[17] with retention of stereochemistry at C^1 and C$^{1'}$ (C^4 and C^3 in **3**) (Scheme 9). On the other hand, (1*R*,1′*R*)-**2** provides intermediate *epi*-**vi** having severe 1,2-repulsion between the *n*-Bu and R group. Therefore, its α-amino carbanion center was epimerized to form stereochemically favorable *ent*-**vi** which undergoes cyclization to provide (3*R*,4*R*)-**3**.

In summary, we have described a diastereoselective approach to tetrahydroisoquinolone by the ring-enlarging reaction of phthalimide-derived hemiaminals. Further studies on the scope and limitation of this reaction as well as its synthetic applications are now under way.

Acknowledgment

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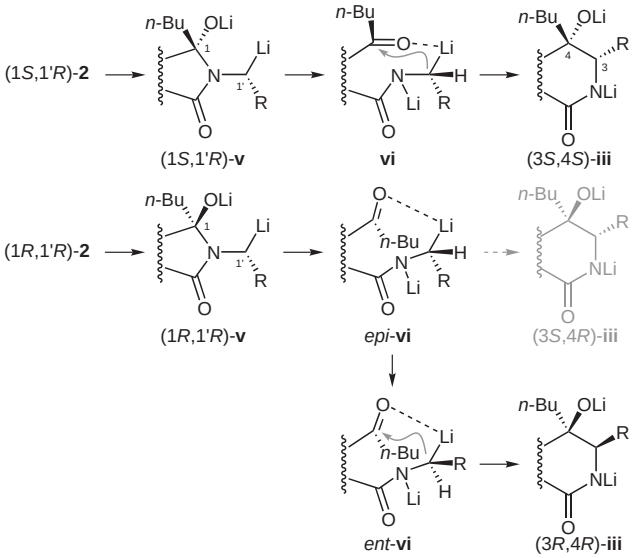


Scheme 9

References and Notes

(1) (a) Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004**, *104*, 3341. (b) Briet, N.; Brookes, M. H.; Davenport, R. J.; Galvin, F. C. A.; Gilbert, P. J.; Mack, S. R.; Sabin, V. *Tetrahedron* **2002**, *58*, 5761.

(2) For recent studies of the asymmetric synthesis of tetrahydroisoquinolones, see: (a) Vicario, J. L.; Badia, D.; Carrillo, L.; Anakabe, E. *Tetrahedron: Asymmetry* **2003**, *14*, 347. (b) Derdau, V.; Snieckus, V. *J. Org. Chem.* **2001**, *66*, 1992. (c) Davis, F. A.; Mohanty, P. K.; Burns, D. M.; Andemichael, Y. W. *Org. Lett.* **2000**, *2*, 3901. (d) Davis, F. A.; Andemichael, Y. W. *J. Org. Chem.* **1999**, *64*, 8627. (e) Clark, R. D.; Souchet, M.; Kern, J. R. *J. Chem. Soc., Chem. Commun.* **1989**, 930.

(3) (a) Tomoyasu, T.; Tomooka, K. *Synlett* **2004**, 1925. (b) Tomoyasu, T.; Tomooka, K.; Nakai, T. *Tetrahedron Lett.* **2003**, *44*, 1239. (c) Tomoyasu, T.; Tomooka, K.; Nakai, T. *Tetrahedron Lett.* **2000**, *41*, 345. (d) Tomoyasu, T.; Tomooka, K.; Nakai, T. *Synlett* **1998**, 1147.

(4) The ring-enlarging reaction of the phthalimide-derived enolate is well established as the Gabriel–Colman rearrangement; see: Allen, C. F. H. *Chem. Rev.* **1950**, *47*, 275.

(5) All the compounds were characterized by ^{1}H and ^{13}C NMR analyses (recorded in $CDCl_3$ unless specified otherwise). Data for selected products follow.
(1*R**,1′*R**)-**2**: ^{1}H NMR (270 MHz): δ = 7.71–7.67 (m, 1 H), 7.52–7.40 (m, 3 H), 7.25–7.09 (m, 5 H), 3.23 (dd, *J* = 9.2, 5.3 Hz, 1 H), 2.70–1.90 (m, 6 H), 1.61–0.79 (m, 34 H). ^{13}C NMR (67.5 MHz): δ = 166.8, 146.5, 141.9, 131.8, 131.6, 129.6, 128.3, 125.8, 123.0, 121.7, 92.8, 38.7, 35.8, 34.6, 29.3, 29.1, 27.6, 25.9, 22.6, 13.7, 11.4.
(1*S**,1′*R**)-**2**: ^{1}H NMR (270 MHz): δ = 7.75–7.72 (m, 1 H), 7.52–7.45 (m, 3 H), 7.30–7.17 (m, 5 H), 3.43–3.35 (m, 1 H), 2.80–2.51 (m, 3 H), 2.18–1.90 (m, 3 H), 1.65–0.74 (m, 34 H). ^{13}C NMR (67.5 MHz): δ = 167.1, 146.2, 141.7, 131.7, 129.6, 128.3, 128.2, 125.9, 122.8, 121.6, 91.9, 39.1, 36.0, 34.7, 29.3, 29.1, 27.5, 26.1, 22.5, 13.6, 11.1.
3: ^{1}H NMR (270 MHz): δ = 8.03–7.99 (m, 1 H), 7.57–7.48 (m, 2 H), 7.42–7.34 (m, 1 H), 7.27–7.11 (m, 6 H), 6.83 (dd, *J* = 14.3, 4.8 Hz, 1 H), 3.41 (td, *J* = 7.9, 2.8 Hz, 1 H), 2.84–2.75 (m, 1 H), 2.66–2.55 (m, 1 H), 2.28 (s, 1 H), 2.18–2.07 (m, 1 H), 2.02–1.92 (m, 1 H), 1.87–1.75 (m, 1 H), 1.65–1.52 (m, 1 H), 1.39–1.04 (m, 4 H), 0.81 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (67.5 MHz): δ = 164.8, 143.2, 141.0, 132.5, 128.6, 128.5, 128.3, 127.8, 127.6, 126.6, 126.1, 124.4, 74.1, 58.8, 40.8, 32.2, 31.6, 25.4, 22.8, 13.9.
5a: dr = 85:15. ^{1}H NMR (300 MHz): δ = 8.10 (d, *J* = 7.5 Hz, 1 H), 7.65–7.35 (m, 3.90 H), 7.20–7.15 (m, 2.58 H), 7.07–7.04 (m, 1.71 H), 6.64 (br s, 0.85 H), 6.36 (br s, 0.15 H), 4.86 (s, 0.15 H), 4.64 (d, *J* = 4.5 Hz, 0.85 H), 2.31 (br s, 0.15 H), 2.05–1.97 (m, 1.85 H), 1.90 (br s, 0.85 H), 1.57–1.40 (m, 0.85 H), 1.57–1.07 (m, 3.15 H), 1.06–0.95 (m, 0.15 H), 0.86 (t, *J* = 7.5 Hz, 2.55 H), 0.68 (t, *J* = 7.5 Hz, 0.45 H). ^{13}C NMR (75 MHz): δ = 166.43, 165.10, 143.89, 142.89, 136.73, 135.56, 132.72, 132.25, 128.74, 128.58, 128.51, 128.46, 128.00, 127.86, 127.70, 126.63, 125.40, 125.13, 74.54, 73.61, 65.78, 63.74, 41.66, 34.72, 29.70, 25.82, 24.88, 22.89, 14.06, 13.96.
5b: dr = >95:<5. ^{1}H NMR (300 MHz): δ = 8.10 (d, *J* = 7.5 Hz, 1 H), 7.57–7.50 (m, 2 H), 7.45–7.40 (m, 1 H), 7.30–7.26 (m, 3 H), 7.22–7.19 (m, 2 H), 6.40 (br s, 1 H), 4.61 (d, *J* = 3.3 Hz, 1 H), 2.08 (s, 1 H), 1.67 (s, 3 H). ^{13}C NMR (75 MHz): δ = 65.17, 143.70, 136.58, 133.36, 128.83, 128.75, 128.70, 128.30, 128.11, 126.67, 124.14, 71.21, 65.50, 28.33.
5c: dr = >95:<5. ^{1}H NMR (270 MHz, DMSO-d_6): δ = 8.22 (d, *J* = 3.1 Hz, 1 H), 7.98 (dd, *J* = 7.3, 1.8 Hz, 1 H), 7.54–7.46 (m, 2 H), 7.26 (s, 5 H), 7.16–7.04 (m, 6 H), 6.14 (s, 1 H), 4.98 (d, *J* = 3.1 Hz, 1 H).
5d: dr = 58:42. ^{1}H NMR (300 MHz): δ = 7.97 (d, *J* = 7.2 Hz, 0.42 H), 7.69 (d, *J* = 7.2 Hz, 0.58 H), 7.53–7.30 (m, 5 H), 7.25–7.14 (m, 3 H), 6.51 (br s, 0.58 H), 6.25 (br s, 0.42 H), 4.88–4.74 (m, 2 H), 2.71 (br s, 0.58 H), 2.18 (br s, 0.42 H). ^{13}C NMR (75 MHz): δ = 166.02, 165.96, 139.24, 138.90, 138.51, 136.61, 132.99, 132.81, 128.98, 128.80, 128.58, 128.19, 128.04, 127.83, 127.41, 127.17, 127.07, 71.68, 69.24, 62.48, 60.33.

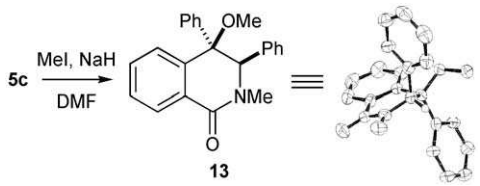
(6) The diastereomeric ratio was determined by ^{1}H NMR analysis.

(7) Bisagni and co-workers reported a similar tetrahydroisoquinolone synthesis involving the dilithiated intermediate, see: Delcey, M. C.; Huel, C.; Bisagni, E. *Heterocycles* **1995**, *41*, 1721.

(8) The exact origin of the observed high reactivity of MeLi compared with that of *n*-BuLi is not clear at present, though it might be considered as the result of a difference of their aggregation states.

(9) **Ring-Enlarging Reaction; Typical Procedure:** To a solution of hemiaminal **6b** (61 mg, 0.24 mmol) in anhyd THF (10 mL) was added MeLi (1.04 M solution in Et_2O; 1.15 mL, 1.20 mmol) dropwise at –78 °C under an argon atmosphere. The resulting mixture was stirred at –78 °C for 30 min and then the temperature was allowed to rise to 0 °C over a period of 30 min. The reaction was quenched with a sat. aq solution of NH_4Cl. The aqueous layer was extracted with EtOAc. Then, the combined organic layer was washed with a sat. aq solution of NaCl, dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure. Purification by silica gel chromatography (hexane–EtOAc, 3:1) gave 56 mg (91%; dr 93%) of tetrahydroisoquinolone **5b**.

(10) The relative stereochemistry of **5c** was determined as *syn* by X-ray crystallography of its dimethylated derivative **13** (Scheme 10). The stereochemistry of tetrahydroisoquinolones **5a**, **5b**, and **5d** was speculated as *syn* based on its similarity with **5c**. Crystallographic data for **13** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC 610566. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (deposit @ccdc.cam.ac.uk).



Scheme 10

(11) Reviews on aza-Wittig rearrangement: (a) Tomooka, K. In *The Chemistry of Organolithium Compounds*; Rappoport, Z.; Marek, I., Eds.; John Wiley & Sons: New York, **2004**, 749. (b) Vogel, C. *Synthesis* **1997**, 497.

(12) Generation of the benzylic anion was confirmed by a trapping experiment using TMSCl.

(13) DFT calculations were performed at the B3LYP/6-31+G(d) level with Gaussian 03 on TSUBAME system at Tokyo Institute of Technology. To simplify the calculation the possibility of the aggregation was not considered. The sum of electronic and zero-point energies was used as the energy values in Figure 2 and Scheme 7.

(14) The enantiopurity of **3** was determined by HPLC analysis using a Sumichiral OA-3200 column.

(15) It has been reported that the α-amino benzylic carbanion is stereochemically unstable; see: Hoffmann, R. W.; Ruhl, T.; Harbach, J. *Liebigs Ann. Chem.* **1992**, 725.

(16) Stereochemistry of the major epimer of **2** (dr = 69:31) was assigned as (1*R*,1′*R*)-isomer based on a correlation with the vinyl analogue. The reaction of (*R*)-**1** with H_2C=CHMgBr provides (1*R*,′*R*)-isomer as the major epimer (dr = 83:17) and its stereochemistry was unambiguously determined by X-ray crystallography. The detailed result as well as a ring-enlarging reaction of a vinyl analogue will be reported elsewhere.

(17) The absolute stereochemistry of **3** was speculated based on the reaction mechanism.